Shroff, Hari 2020

Dr. Hari Shroff Oral History

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Hari Shroff by David Zierler

National Institute of Biomedical Imaging and Bioengineering, NIH

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DAVID ZIERLER: OK. It is March 10th, 2020. This is David Zierler, oral historian for American Institute of Physics, and it is my great pleasure to be here with Dr. Hari Shroff. Thank you so much for your time today. This is really exciting for me.

HARI SHROFF: Thank you. Yeah.

ZIERLER: So would you just state your title and affiliation with NIH just so everybody knows where you're coming from?

SHROFF: Sure, yeah. Yep. So I'm a senior investigator in the National Institute of Biomedical Imaging and Bioengineering or NIBIB within the NIH. So this is sort of like being a tenured professor at a university. And I also direct an advanced imaging resource here at NIH to try and disseminate imaging tools to the broader biological community at NIH.

ZIERLER: OK, all right, so what I'd like to do is I take us all the way back to the beginning.

SHROFF: [laugh] OK.

ZIERLER: So tell me about your family, where you were born, early childhood.

SHROFF: I was born in a tea plantation in India. My parents were both medical doctors on another tea plantation, and so when I was born, they drove me to a hospital nearby. And then for the first year of my life I was in India, and then my parents moved to England. There were better opportunities for them there in their professions. And so from one to nine, I grew up in England. My brother, my younger brother was born there. And then in '91, my family moved to the US to Cleveland, Ohio. My dad got a job at the Cleveland Clinic for a year, and the idea was always to move out west because my mother has a bunch of family in Seattle area. So I was in Seattle from 10 until 19. I went to college there and then went to UC Berkeley for grad school and then came out to the east to Virginia to do a post-doc at Janelia Farm, and then I've been at NIH after that. So since 2006 I've been in the DC area.

ZIERLER: OK. So let's—that's a good overview. Let's rewind right back to the beginning. Medical doctors on a tea plantation. What does that mean? Meaning they're administering to the people who are working there? They're the doctors for those workers?

SHROFF: That's correct. So they met in medical school, which was funded by the Indian army. And so they had some stipulation that after medical school they had to go and be in an army post. So one of the—

ZIERLER: Like a national service kinda thing ?

SHROFF: Something like that. Exactly, yeah. So after this, they both got jobs at this tea plantation, this hill station, and yeah, I think at the place they were at, they were the only doctors around. And so they sort of had this loose connection of other contacts from their medical school days, but from what I understand, there was no major hospital where they were. So my mom had to travel hours, I think, to have me in a hospital setting.

ZIERLER: Uh-huh. So they were not—they must have been general practitioners. They couldn't have been specialists in that setting, I assume.

SHROFF: At that time, I think that's right. Well, my dad is an anesthesiologist, so I think he was probably administering anesthesia. My mom was actually an eye doctor, ophthalmologist at the time.

ZIERLER: OK, and your last name Shroff?

SHROFF: Shroff, yeah.

ZIERLER: Doesn't sound like a classical Indian name.

SHROFF: Yeah, that's true, and in fact most people spell it incorrectly. They put a C in there because there's this tendency to assume it's German.

ZIERLER: Like a German kinda spelling, right.

SHROFF: I think what happened is that it might have at some point been anglicized from Saraf [?], which is a traditional name where my dad is from is Rajasthan, but I don't know that for sure. Yeah, they've been Shroffs for a while back.

ZIERLER: [laugh] OK. And so then England, and who got the job in England?

SHROFF: Both my parents got jobs in England.

ZIERLER: They did.

SHROFF: Yeah.

ZIERLER: They did.

SHROFF: And I think the system was a bit different in India and England, so they had to do residencies first in England, both of my parents. And then they transitioned to kinda full-time staff. But they—none of us particularly liked [laugh] England, and so—

ZIERLER: You have memories of England?

SHROFF: I have memories of England, many good, some not so good. It was kind of a difficult time growing up a little bit. There was some—

ZIERLER: And what years are we talking about here?

SHROFF: This would have been ’83 to ’91. And we moved around a bunch in England, so I lived in Birmingham, which is a fairly well-known kind of industrial city, and then some smaller towns such as Stoke-on-Trent. That's one of them that I remember. And school was kinda difficult for me in England because of discrimination in some of the places.

ZIERLER: Really?

SHROFF: Yeah, so this term Paki, which is a derogatory term used for Pakistani, was something that I remember being called as a kid, and so I was not a happy camper.

ZIERLER: Hey, I’m Indian. Wait a minute. [laugh]

SHROFF: Yeah, exactly. I was Indian, but in general, that was kind of unpleasant. And my—I think my parents also felt there was kind of a ceiling to what they could do in England.

ZIERLER: Yeah, yeah. Now, we’ll get to the circumstances leading to you entering undergraduate as a 14-year-old. But during your formative early years in England, are there already trend lines which are suggesting that you are sort of intellectually on a fast track, or do you remember any of those conversations?

SHROFF: I think the schooling was—at least at the early levels—more intense in England than the US, and so that's one factor that might have contributed. When I came to 4th grade in Cleveland, Ohio, I knew—

ZIERLER: You were just more far along.

SHROFF: I was just more far along because of the curriculum, so that was part of it. And then my parents spent a lot of time with me as a kid, so I remember learning multiplication tables at a very early age and learning how to read early. And so I loved to read as a kid, and we didn’t have a TV, so that might have contributed to a bunch of reading. But other than that, I don’t remember much about an accelerated program. I enjoyed school. I enjoyed learning about stuff, and my parents took care to spend a lot of time with us on—sort of talking about education things, going to fields and looking at animals and making sure there were always resources available for our education. But we went to public schools. There was no gifted program in the schools, yeah.

ZIERLER: Yeah. And then headed to Cleveland Clinic. What is the opportunity there for your father?

SHROFF: So my father got a good job at this Cleveland Clinic as an anesthesiologist, and I think it was just sort of a step-up from what he was doing in England. I think he was practic…

ZIERLER: He’s in operating rooms? That's what he’s doing?

SHROFF: He’s an anesthesiologist, so he’s giving people medicine before the surgeon operates on them. Yeah, and I think it was sort of a good environment for him to be in, but I think the intention even then was just an intermediate position. This was not a permanent position or anything like that, and—

ZIERLER: It got them into United States.

SHROFF: Exactly, got them into the United States, and then one year after that, he got a job at University of Washington as a professor there of anesthesiology. And—

ZIERLER: And your mom’s thrilled ‘cause that's where family is?

SHROFF: That's where family is. In fact, my mom stopped working for a while when we got to the US. It’s actually an interesting story there, which we can touch on if you’d like. Well, she—

ZIERLER: Please, go for it.

SHROFF: My dad had a bad rock climbing accident when I was 12 or something, and there was some danger that he would no longer be able to use his wrists—

ZIERLER: Oh.

SHROFF: —and really bad. He had to get bone grafts from his hips to replace—he had pin—metal pins in his hands, and so there was some danger that he wouldn't be able to practice because he needs his hands. So my mom went back to residency in South Dakota of all places. That was the only place she could get a residency after being out of it for a while. So she retrained as an internal medicine doc over there for three years when my brother and I were growing up. And so then she went back to work, and my dad fortunately is fine. So he was able to go back to doing anesthesiology, but that was sort of a brief hiatus in Seattle. [laugh]

ZIERLER: Did they have to do the long distance thing when your mom was in South Dakota or—

SHROFF: They did. They did. So that was difficult for us because we would be in school in Seattle while my mom was in South Dakota, and we would go and visit her for the summers. So I learned how to drive a little bit early in South Dakota because of all the farm stuff, right? So you can get your permit when you're 14, I think, over there and—but it was difficult for my brother and I. We—yeah, it was weird when she came back to have our mom there all the time for a little while [laugh] before we adjusted. So it was a difficult time, and for our dad too, right? He was essentially functioning as a single parent while also working.

ZIERLER: Were you able to rely on your mom's extended family in Seattle?

SHROFF: That really helped in fact. Yeah, so they would look after us and sometimes pick us up from school and so on while my dad had to work. Yeah.

ZIERLER: Now, establish the sorta trend line to you entering an undergraduate experience at age 14. What are the considerations for and against in terms of making this kinda decision?

SHROFF: So I think certainly when I came to the US, I remember being bored in school. I loved school, but there were—perhaps because of the England experience, I was kind of ahead of everybody else in terms of the math and certainly the reading that I could do. And so my parents put me in these gifted public school programs in—when we got to Seattle, there were these programs, and those were great for me. I felt like there were other similar kids there. But then I went to a public middle school where again it seemed like I was in a gifted program for three of the periods or something, but I remember being kinda bored. And then as luck would happen, one day—this was when my mom was in South Dakota——I brought home the school newsletter, which I never read, and my dad noticed an ad for this program in University of Washington. So there's this early entrance program that has been around since the late 70s founded by a professor at University of Washington and his wife who also is a professor, and these guys studied gifted children. This was their research area. So they started this program which was the first of its kind, I understand, in the US. Now there are others of them scattered around, but what made this program unique is that there's a transitional program where you spend one year after 7th or 8th grade doing this intensive program where while you can't possibly go through high school in one year, but they do an awfully good job preparing for—academically for college. So if you pass through this very rigorous program, you can then go to U-Dub as a full-time freshman. And so—

ZIERLER: Are you living at home or you're living on campus?

SHROFF: So most of us live at home because parents feel very uncomfortable with their kids—

ZIERLER: Of course.

SHROFF: And so [laugh] I lived in the woods in—by this point near Seattle. My parents lived in this small town 30 miles east of Seattle. And I couldn't drive, so I—every day I spent an hour and a half commuting to campus each way, which sucked, until I was 16, and then I could drive. But then my brother got into the same program, so then I had to drive him back and forth for a while. So it wasn't actually that much fun, but I'm kind of jumping ahead. So anyway, my dad found this advertisement that he told me about, and I thought this was the most awesome thing. I couldn't believe that such a thing existed, so we went to visit—

ZIERLER: So you were looking—you were excited about the prospect of leaving high school early?

SHROFF: I was definitely excited. In fact, I—this isn't very mature, but as soon as I heard about it, I couldn't imagine not doing this. It sounded so much better than what I was doing at the time, and so I really wanted to go and check it out. And so there was interview—

ZIERLER: Mostly 'cause you were bored in class? Is that the big push factor there?

SHROFF: I think that was a push, and it just sounded like an awesome thing to be able to accelerate that much. I was—I love to do—to learn stuff. I still love to learn stuff, but at that time, I was just—this sounded like a great opportunity. You could take college classes. There was so much to know and so on. And I was on a swim team, and I played the flute. These are two of my big outside interests, and of the two, I was much more into my—into the flute. And swimming—so I sort of—once I learned about this program, it became clear that for this transitional year, you'd have to give up lot of other stuff, right? And I was kind of prepared to do that as well as I learned more and more about it. And then I visited the program. So they have this extensive interview process where first you go and sit in on like a day so you can sort of see what this environment is like and the small classroom on the University of Washington campus where they have professors come to you, and you learn these four subjects, precalculus, English, history, and physics. And so I thought this was great observing the kids and how they interacted. It's a small class. So 15 or 16 kids, and—

ZIERLER: And your classmates are also your age? They're peers?

SHROFF: Exactly. They're all 13 and 14. And so listening to those kids and seeing the level of instruction that they were getting, I thought this was, again, awesome. And so I—the—you had to take the SAT and something called the Washington precollege test, which I did, and then you had to interview. So all of that went well, and I got a position. And then there was this argument with my parents. So my mom definitely did not want me to do this. She thought that I wouldn't be ready for it, and I think it was my dad who kind of convinced her—

ZIERLER: Intellectually, socially, all of the above?

SHROFF: Both I think, yeah. She was—I overheard them one day speaking about this. My mom felt that intellectually also—she was like, "Hari's precocious, but I don't think he's ready for this."

ZIERLER: He's no genius. [laugh]

SHROFF: Yeah, exactly. Yeah, so that made me all the more determined to kind of convince them that I—but I think what convinced her is when she came for this interview process. They also interview the parents, and she talked to the staff there, and then they—so again, this program is unique because they have a psychologist there. They have peers that you—that are your age that have gone through the program, and they have space for you to be there in addition to being a freshman or whatever, right, and participating in the classes. There is this kinda space where you can be basically a teenager, right, and talk to people. And so I think she saw that and the—this program had been going on for decades by this point. They had a track record of success of people going through it and being successful, right? And so she sort of was convinced that—to let me try it. Yeah, so that's kinda how I got into it. It was a bit of luck in a sense that I found out because of this newsletter, and then once I found out, I was kinda totally into the idea. And I definitely didn't have the maturity to think about the opportunity cost of doing this at that time. It just didn't occur to me at all to be concerned maybe because I was a nerd and because my friends were mostly people that liked to study and learn stuff anyway. I had a few outside interests but not—my peer group in middle school was not huge. I had a few close friends that I would hang out with and do sorta the usual teenage stuff with like board games, videogames, playing outside in parks, building fireworks, this kinda thing, but I was not like a jock, and I didn't have this extensive investment into my middle school. My brother did, on the other hand. He went to high school for a year. He skipped a bunch of years before this, and he really enjoyed high school but also felt that he wasn't being challenged in the local town high school. So my experience was different than his in that I just—I really didn't pause to think about this question, right? And now whenever I tell people about this, their first impulse is always, "Well, what about your friends, and what about the high school experience?" And I went to my high school prom or the prom that I would have gone to. I kept in good touch with my middle school friends, but it just wasn' t for me. This was the right thing for me.

ZIERLER: So is the program—does it transition you into a normal campus environment the subsequent years, or are you basically doing four years of college from age 14 to 18 with your peers?

SHROFF: It transitions you into a normal college environment. So in this transitional year, in that year, you're mostly in this classroom that is in a building away from the other buildings on campus with just these 13 and 14-year-olds and the faculty. And in the last quarter of that system, you take a college course to sort of integrate fully—more fully into that experience. But then if you pass this transitional year, you're taking classes like a freshman. You can sign up for the full complement of classes, and of course your home situation is unique, right, because you're young. And there have been a few cases, exceptional cases where these kids at that stage move into the dorms, but that's—generally, it's an exceptional case like maybe the parents are living in one of the islands, right? So Washington state has these islands where you take ferries. It would—that would be even less practical than the bus, and so those guys find some way of doing it. My brother, in fact, made some deal with a French family to watch their kids on the weekends, and then he would stay not in a dorm but within walking distance of campus the last two years. But in my case, I—my parents insisted that I stayed at home, and I kind of resented that. I wished I could have spent more time closer to campus. A couple of nights a week later on as this progressed I would stay with my mom' s extended families who lived closer to campus. So that would cut the commute down. Instead of an hour and a half, maybe it would be like a 20-minute bus ride. But they sort of insisted that I would stay with family, and looking back on it, of course that changed the dynamics of my college experience, right? My peer group was mostly the other kids that I knew, but I made a couple of really good normal age college friends as well that I still keep in touch with.

ZIERLER: Interesting. Interesting.

SHROFF: So unique experience, and since going through this program, now that same program has a—sort of a gentler, let's call it, experience for people that go through, I think, 10th grade. So then it's just a two-year transition, which is maybe more manageable. You're a little bit older. You look more like a college age 18-year-old. But I have to say that one thing that made it easier was the fact that University of Washington is huge. So this is not a small liberal arts school experience. At least in the beginning, your classes are large, right, like the entry level physics classes and so on, and so that means that unless you're very—unless you make a big deal out of the fact that you're young, most kids in this program have no problem just integrating in with the rest of the course. And it was always a bit of a shock when people find out, but again, it's a big place, right? You're not running into so much of a social stigma because people have other things to do with their time and so on.

ZIERLER: Sure, sure. So it's hard enough for a 20-year-old, 21-year-old to figure out a major, what are you gonna do when you grow up. Did you feel that pressure as a 14-year-old, 15-year-old like where—what's my next move? How do you conceptualize what your next move is after undergraduate when you're not even 15 years old yet?

SHROFF: I think that it was difficult. It was more difficult in sort of choosing a major because I loved science, but I also like to write. That's something that I found out in the course of this transitional year, and so I was—for me, the initial question was what major to pick. And I ended up in sort of this jack of all trades major bioengineering because there was some physics, some chemistry, some engineering. I couldn't make up my mind as to which discipline in particular. So that was difficult. And then I got into a research lab early, which was also very helpful because that—you learn pretty quickly that doing research is different than learning about research when you're working in a lab. And I was super lucky to have awesome undergraduate mentors who helped with that. I could work closely with graduate students as an undergrad, and that made a huge difference. I was pretty—I don't know what the right word is, but I didn't really know much about graduate school until like the last two years of college. I didn't—that wasn't really on my radar until fairly late in the game, and then I kinda like looked intensively into that aspect. But I wasn't thinking super, super far ahead when I got in. I was thinking about the next step.

ZIERLER: Now, with your parents both being doctors, did you—growing up, was there sort of an expectation that you would enter the sciences or not really?

SHROFF: Not really. My parents were very good about that. They were not the stereotypical Indian family in that respect as far as you must be an engineer or doctor or lawyer something or—they were—I think the one thing they said is they thought they would—they mentioned to me once they thought I'd make a good doctor. But otherwise, they were very good about letting me just do my own thing, and so that's something that was never really a pressure point. I mean, it was more like thinking what is it that I—am I kind of locked into this major choice. I—the one thing I remember is not wanting to waste a lot of time in one major and then deciding it wasn't for me and then switching. And as it is, I took five years, which is a bit long. I—the bioengineering degree at that time in U-Dub was kind of a make-your-own major, and so most people took a little bit longer than the four-year major. But I remember being kinda conscious of that, not wanting to spend too much time casting about.

ZIERLER: Bioengineering was its own department, or it was sort of a cut and paste from different departments?

SHROFF: At the undergraduate level, it was more of a cut and paste thing. Now it's become a much bigger thing at the undergrad level, but at the time they were admitting three, four undergraduates a year. It was mostly a graduate department. And so in some ways that worked in my favor because I was able to do undergrad research in the chemistry department, and bioengineering folks didn't bat an eye about that. They were happy, I think, as long as I found a home, research home.

ZIERLER: So what are the core subjects for bioengineering? You're taking physics, chemistry, biology, and engineering?

SHROFF: Yeah, yeah, but not in any great depth, which is something that I regret a little bit. I ended up filling in more physics at Berkeley 'cause I was interested in physics. I became more and more interested in doing physics. As I did research, I began to sorta see that if I could understand physics, then this kind of opened doors, right? If there was a way of—if I could master, for example, math and physics, then I could do lots of things with those things.

ZIERLER: Because it's foundational.

SHROFF: It's foundational, and the biochemistry that I took as an undergraduate made it easier in Berkeley because the molecular biology stuff was less of an alphabet soup. I already knew what an amino acid was, what a protein is, the central dogma of biology and all the things that I learned as an undergraduate. But I didn't—I sorta felt later on that I was missing some physics, and so I ended up trying to take some of that in grad school.

ZIERLER: Right. And what about the engineering aspect? Where did you learn how to tinker and put stuff together?

SHROFF: So the—also mostly in research. So I took some undergraduate engineering labs like thermodynamics is one thing that I sort of gelled well with the physical chemistry. I took that class from an engineering perspective where we talked about heat engines and building kinda functional devices. But in answer to your question, really research is when I learned how to do that because I worked for an analytical chemist. So he was—he had this crazy idea of trying to measure the pressure generated by a honeybee in hovering flight. He had developed this pressure-sensitive paint that Boeing used. So he had patented this invention, and he wanted to, as his last hurrah before retiring, try and shrink it down to a honeybee. And so it was my job to take this chemical compound and then figure out how to paint it on a honeybee and build an instrument that we could use to kind of measure this—

ZIERLER: A real actual honeybee?

SHROFF: A real actual honeybee.

ZIERLER: [laugh]

SHROFF: So I went around catching honeybees until I found a beekeeper. So that was pretty crazy, but that's really where I got it. I kinda feel like this tinkering stuff—maybe it's different if you're a physics undergrad and you have lots of labs, but I sorta feel like in at least the biological sciences, you get a bunch of lecture material, and you learn about these awesome discoveries that were made, right, like the discovery of kinda the structure of DNA and related experiments. But you don't really get a chance to do a lot of that. The lab courses were kinda contrived I felt like as an undergrad, so I really kinda fell in love with research as an undergrad. That was really a formative thing for me.

ZIERLER: Now, the summers are you active too? Are you normal kid summers, camp, swimming—

SHROFF: Summers I'm active too. In fact, summers are a better time to do that because you don't have the distraction of courses so much.

ZIERLER: Right, and you're on campus the whole time?

SHROFF: Yeah, yeah, yeah.

ZIERLER: New research projects each summer, or you return back to a previous project?

SHROFF: Mostly I just worked with this one guy, this chemist, Dr. Jim Callis. So I started out doing a totally different project. He had some molecular structure modeling using a chemistry tool that does quantum chemistry calculations. So I ended up spending some time doing that, which got boring quickly because it was sort of sitting in front of a computer and running simulations on a program. And then we—I think once I kind of showed him that I was—I could do some good stuff, then he sort of transitioned me into this other project which was much more interesting.

ZIERLER: And so you're five years in, you're 20 years old?

SHROFF: 19.

ZIERLER: 19. Is there an undergraduate thesis that you did or just a culmination of coursework?

SHROFF: Sort of. So I ended up—I don't know if there was a formal undergraduate thesis, but I ended up writing a paper which was kind of, sort of like an undergraduate thesis.

ZIERLER: On what? What'd you write about?

SHROFF: On actually the device that I had built to measure—to characterize the thin films of pressure-sensitive paint. So this was actually—I can't remember who had the idea. Probably wasn't me. It might have been my advisor or somebody else in the lab. But we—in order to see if this paint was—if we could sort of sensitively measure the kind of pressure generated by a honeybee, we needed a way of testing this in an in vitro setting. So we took a long tube of PVC piping and then stuck a thin film of this paint at one end and then used a speaker to kinda—to basically project sound waves on this paint of an amplitude similar to the kind of pressure developed by a bee, and that's something that I built. So I wrote a paper on that with a graduate student. So there were no honeybees in that, but it was still a useful exercise to go through and get it published and all of that.

ZIERLER: It was published?

SHROFF: It was when I—yeah, it was submitted, I think, when I was an undergrad and then published when I was a graduate student, yeah, in some journal of chemistry or something.

ZIERLER: OK, and so when are you planning your next move after undergraduate? What's that process like?

SHROFF: So I—even though the experiments of the honeybee is never materialized when I was an undergraduate student, and it turned out later they were a failure—building a microphone is one thing, but then building an actual apparatus to measure the bee as it flies is much more difficult than that—but I became really interested in insect flight and the mechanics of insects. And so I went to Berkeley partially because there was this guy Michael Dickinson who later won a MacArthur award for doing insect research on fly wings. So I went to Berkeley and interviewed with him as part of the biophysics program along with other biophysicists. And so I—

ZIERLER: So you knew you wanted to do biophysics?

SHROFF: I knew I wanted to do biophysics. In fact, the advice that I got from my mentors at University of Washington was “Forget the engineering and tool building. Try and learn some science. Go into that. Try and learn about the physics of what’s going on.” And so that sort of influenced my decision to go into a biophysics program.

ZIERLER: Now, at Berkeley, is the biophysics—is it its own program, or it’s a subset of the physics department?

SHROFF: It’s a center which feeds into many departments including physics, and that's another thing that attracted me about it. I wasn’t sure about what I wanted to do in graduate school. That was in fact to me much more of a—it was much more of my radar at that time than the undergraduate decision. And so I—what appealed to me about Berkeley biophysics is that it was super broad. There were like 90 faculty from lots of different departments, and they had a rotation scheme that you could try out different labs during the first year. That really appealed to me. So I—this insect stuff was one thing, but also at the time, people were very interested in making measurements on single molecules. And so there was this leader in that field Carlos Bustamante at Berkeley who I also interviewed with. So there were a couple of different threads that made Berkeley very appealing, and it was mostly the breadth of the program.

ZIERLER: So you’re 19 years old when you enter?

SHROFF: Yeah.

ZIERLER: So no break in between? You go straight in?

SHROFF: Go straight [laugh] in.

ZIERLER: Wow.

SHROFF: Yeah.

ZIERLER: Now, at this point, are you starting to think more along a career like where this is all headed, or this is still purely an academic pursuit, you’re just seeing semester by semester?

SHROFF: I think at that point, it was still just a short term thing. I wasn’t thinking long term at that point either. Yeah.

ZIERLER: And so at what point did you settle in on a dissertation topic?

SHROFF: So after doing this rotation system, I ended up working with not this guy Bustamante but one of his former post-docs, Jan Liphardt, who got a faculty position at Berkeley. And so I really wanted to do instrumentation. In fact, the insect research stuff got—that got tanked in a hurry because Dickinson moved to Caltech. So he told me actually not to go with him. He said, “Learn something new at Berkeley, and if you’re still interested in insects, come to Caltech later for a post-doc.” So that really set me in a totally different area. I wanted to build optical instruments. That's one of the things I enjoyed doing at U-Dub

ZIERLER: But instrumentation—they told you at U-Dub not to go into tool making. [laugh]

SHROFF: They did. They did. They did. They did. Yeah, yeah, they told me not to do it, but I was—

ZIERLER: You didn’t listen.

SHROFF: I didn’t listen, and part of it was that for the single molecule stuff, which was kind of exciting at the time, there were lots of people in this area. It was kind of a hot new area. The idea of watching a molecular motor move on a strand of DNA was super appealing, right? Actually, when you think about it, just the fact that you can monitor a molecule of anything is amazing, right, even—so that was kind of intriguing to me, this idea that you could just understand something fundamental about this molecular machine built using an instrument. And it was also clear to me at that point that you had to build sophisticated instruments to do the science, right? That was an integral part of this kind of biophysics. So I kind of joined this guy Jan Liphardt’s lab with a goal of doing something in this area, and what I sorta quickly realized is that people in this—in these labs were publishing Nature and Science papers all the time, but it was almost like stamp collecting. You would pick—there was a recipe. You would pick your favorite molecular motor, put it in one of these optical traps, and if nobody had characterized the step size or the motion of this thing, then it was like bam, an instant paper. And that had no appeal to me. I didn’t want to be—I was interested in the instrumentation, but I wasn’t that interested in doing that. It started to become clear to me, I think, at that point, that in order to do something new, I had to branch out a little bit from this kind of machine. Is this sort of making sense?

ZIERLER: Of course, yeah.

SHROFF: Yeah, so I was looking around for something to do that was a little bit different in the space, and what sort of occurred to me is that everybody was doing in vitro experiments. So they would take a—it was a reductionist physicist approach. You would take some molecule of interest to a biologist, take it out of the cell, purify the protein and put it into one of these sophisticated machines like an optical trap, and then pull and pull and stretch this machine to understand something about it. I started thinking about, well, could one do this inside living cells. That's something that would be very difficult to imagine doing with an optical trap because anything in the vicinity of the trap sorta gets pulled into the trap. Anything with a refractive index that is higher than the medium gets sucked into this optical trap. And so I started thinking how would one do this kind of measurement, and my mentor at the time, Jan Liphardt, was very encouraging about this. He was like, “Yeah, I think this is interesting, but you’re not gonna be able to get this by building another one of these trapping machines. Maybe there’s another way of attacking this problem.” And so then I—he and I hit upon this idea of designing a force sensor. So the—my PhD dissertation was in making these molecules that could report optically on a local force that was being transduced across the molecule. So imagine you have a spring that is sensitive to force by the displacement, and you have a way of calibrating that spring. That was sort of at a high level what my PhD thesis was. My spring was a little molecule of DNA that when stretched, basically, parts of the DNA moved further apart, and when relaxed, these parts moved closer together. And by attaching a pair of dyes to two points on my spring on the DNA, I could monitor this optically. So I built an instrument to characterize this force, this applied force versus readout, and that part of it all went well fairly early in my PhD. And then I kind of tanked when I tried to apply this in living cells because I was not a cell biologist. I knew nothing almost about cells, but it became clear that these little molecules would get chewed up by the cell. And so I kind of entered this period of depression in my PhD thesis where I wondered what is the use of this thing. You built this widget that nobody would use. That later shaped my thinking on a lot of the way that I approach science, but finally, I was able to graduate by publishing another paper where we put these little sensors of DNA inside DNA loops. So biophysically, these were kind of interesting and important because in your nuclei, the DNA is looped a lot in chromatin. It’s compacted tremendously from the—if you were to spool the DNA out, it would cover this tremendous distance, but it’s all packed really closely. And it’s thought that molecules have to come in and sort of untangle locally the loops, and these forces are important and so on. So I ended up putting my sensors into these DNA loops and making some measurements and then graduating. But I remember—

ZIERLER: So you hit a dead end with the cell biology?

SHROFF: With the cell biology, I hit a dead end.

ZIERLER: Now, was that because—well, because you lacked understanding or—

SHROFF: Because I lacked understanding. So I was so focused—

ZIERLER: But what if you had taken classes and then you would apply that knowledge to this project? Did you ever consider that?

SHROFF: So it's possible that I think that maybe I would have gotten further. I think I might have had to have been maybe in a different lab for that. So my PhD mentor, to his credit, didn't spoon-feed me throughout any of this, and I remember being for a while furious at this, right, that I have this great thing that I've built. Why won't this guy help me think of an application? And I think one—

ZIERLER: This is part of the training?

SHROFF: This is part of the training. This is part of the training, so—

ZIERLER: It's a productive failure is what it is.

SHROFF: Extremely productive failure because there was a macroscopic failure in the sense that I learned that I had to be the person that came up with the stuff, right, if I was gonna be a scientist, an independent scientist. And then there was a micro failure that was important as far as thinking of new ideas about where to put these sensors. So he was happy to kind of have me in his office and listen to me, but he wouldn't spoon-feed me ideas. It's possible that with a different perspective maybe I would have hit upon a different idea and deployed these in the right way. And later on, that paper from graduate school has been cited a bunch now because the idea is a good idea of using these little molecules to measure force. Now people do that to actually measure forces in cells and on top of cells. They—the trick is you use a protein instead of DNA. So you have to make some changes to the dyes, but the basic idea of stretching a spring to read out a force and monitor the readout optically, that idea actually is—was kind of maintained from that thesis project and is used today. It's just that the details were wrong for that aspect. So it's kind of been funny for me to watch that over—it's been 15 years or something, right, since I left, and the idea did have legs, but it took a while for people to catch up. And it took protein engineers to kind of look at this and sorta think, "OK, how do I make this applicable in a living cell?" I didn't have that idea at the time.

ZIERLER: So this is real collaboration? This is other people using what you created in a way that you did not forecast yourself?

SHROFF: Absolutely, and in fact, other people—not even—some people had sort of realized that I published this work, and they cited it. But other groups, I think, hit upon this independently. They were sorta thinking about the general problem, how do I measure forces inside living cells, and they came to sorta the same solution that I did, right, which is that take away the—use the instrument for readout, but forget about trying to insert something and then measure the force. You have to come up with something less invasive.

ZIERLER: So what was your motivation at the time? Were you really not thinking about practical applications down the line? You were—what were you thinking about in real time? What was your goal?

SHROFF: So I think I was thinking about molecules, about abstracting the problem away from the instrument. I kind of had two goals, one was I didn't want to do what everybody else was doing, build an instrument and apply it to a molecular motor. I couldn't see that working inside a living cell, and I think that's correct. That intuition was correct. So I had the right idea, I think, of taking it into a molecule. It's just that the molecule that I picked was the wrong molecule, and there was a bunch of—

ZIERLER: What was the right molecule?

SHROFF: A protein. A protein molecule would have been right. A lot of the rest of my thinking was also—

ZIERLER: And who would have told you that at the time?

SHROFF: Probably a protein biochemist. So if I—and maybe it was a kinda thing where the—sorta the final answer was too far out. It was like two steps. I—the other thing that I did right was I learned a lot in building this instrument to characterize the forces in an in vitro setting. So that part of my thesis was also right. Other people have done the same thing or something very similar. So they make the molecule. They characterize the molecule using an instrument, and then they go one step further. They engineer the molecule to go inside a live cell. That last piece, it would have been great if I could have pulled that off in my thesis, but I didn't, and it was hard at the time but productive, right?

ZIERLER: So not talking to a protein biochemist at the time, does that speak to larger issues in terms of a lack of opportunities to collaborate, or is that just such a far off concept that you wouldn't have even known who you needed to speak to at the time?

SHROFF: I think part of it was just a lot of things would have had to have gone right in my PhD. There's usual making mistakes during the PhD and failures along the way, right? There were molecules that I made that went nowhere. So—

ZIERLER: Also, you're not 28. You're what, 21, 22, right?

SHROFF: Yeah, yeah, yeah, I guess. Yeah, yeah.

ZIERLER: So there might be some maturity issues—

SHROFF: Yeah, that's true. I think that's true.

ZIERLER: —a worldliness, right?

SHROFF: Yeah, yeah. For example, I got—I turned 21 during my [laugh] PhD, and yeah, yeah—

ZIERLER: Right. You're supposed to be in a frat house when you're 21. [laugh]

SHROFF: That's—maybe that's right, yeah. So there was some of that too. Who knows what might have happened had I had this idea in another lab in a biology department, right? Maybe then I would have gotten the kind of feedback. But I think part of it is also just perspective. As a graduate student, if there's a leap from high school or what I did to college, I would say there's even a bigger leap from college to graduate school, right? And so you're learning how to really be independent and do stuff, right, by yourself. That the goal of a PhD.

ZIERLER: Yeah, and to be able to productively contribute to the field.

SHROFF: Exactly. To do something new. And so I think had I devoted more time, had I stayed in Berkeley for a post-doc and wanted to continue this, maybe I would have gotten further, maybe I would have had the same insight.

ZIERLER: Right. Two questions at Berkeley where you're really starting to tinker at a high level to create new instruments, right? How much of is—of it is you're taking stuff off the shelf and reassembling it in new ways? And how much of it is the stuff doesn't exist yet and you're working with the engineers and the technology people to say, "This is what I need. Can you build this for me?" Or are you building that stuff yourself?

SHROFF: So I would say that I did have to build stuff myself because it wasn't commercially available, but there were publications—the instrument that I built at that time for characterizing these sensors was something that I had to build de novo. There was nothing like it in the world. It was a combination. Part of the instrument applied the force. The other part of the instrument read out the force, and neither was commercial. So I did have to put two things together in a way that was unique, and there were academic publications by others that had done each piece but nothing commercial. So for example, to apply the force, I used a pair of rare earth magnets that I bought from RadioShack that—it was called magnetic tweezers that people were using to stretch DNA. That's how I hit upon the idea of using them, but I had to couple that with a way of reading out the fluorescence, the readout from this force sensor. And there was no commercial way of doing that. So I was lucky to be in an environment where people were doing things like that for other problems. Other people were labeling protein molecules and reading up the fluorescence from single protein. So there were people around me that had done home-built stuff, but there was no prescription. There was no manual saying this is how you do it. So I did have to tinker in a way to do this. That was all something I did myself, and I made lot of mistakes in doing that. And I—but I would say that I—at least as a graduate student, I made a bunch of design choices that were empirical, right? There was nobody—there was no senior mentor at that point telling me, "This is good optical design. This is how you do it." And so as a consequence, as a graduate student, I kind of just bumbled through it enough to kind of make it work. The training on how to do stuff, how to think came later for my post-doc, which I—which we can get into.

ZIERLER: Yeah. So you really didn't take courses in optics?

SHROFF: I didn't. I didn't.

ZIERLER: You're self-taught at this point?

SHROFF: Yeah, yeah, I'm self-taught.

ZIERLER: So how do you know? How you know if you're hitting on something correctly or not?

SHROFF: You read papers. You talk to other people that know more than you, and there were people like that around me. So there were post-docs not in my lab because I was Jan's first graduate student. There were post-docs that came later, but there were other post-docs that were building optical rigs for doing this optical trapping, right? So there was a lot of optics expertise around. Working with lasers is another kinda bread and butter thing, right, in the physics department. So I could ask them for advice, but nobody—to put things together in exactly the way I wanted them, that had to come from me. And so yeah, a combination of reading papers, bumbling, and talking to people.

ZIERLER: Now, at what point do you start to get motivated by the health science research aspect. In other words, this is not just a theoretical issue that you're looking to solve in a lab, but these are things that actually can help people.

SHROFF: I think—so there are different degrees of helping people. I think I was never super worried about the impact I would have on healthcare, on—in other words, I always knew that I wouldn't have the same impact as if I were a medical doctor, right, that any research advance that I made in basic science would be years off. That part didn't bother me, but what did start to—

ZIERLER: But there's also a macro, micro there. As a doctor, you're helping one patient at a time.

SHROFF: There is. There is.

ZIERLER: In the lab, you're creating—

SHROFF: Exactly.

ZIERLER: —protocols that can help everybody.

SHROFF: And that's how I justified it to myself, exactly what you say, this macro thing. But what did bother me was the fact that I built this tool, and I was worried that nobody would use my tool. That was—that became very clear to me as my PhD went on, that if you're a tool builder, you want to at least have the option of building such a thing from the get-go that would have wide impact. And I didn't think that far ahead. I had kind of this lofty goal, right, of building these force sensors and putting them in cells. And this was motivated by the desire to do something that nobody did, nobody could do. But I didn't chain it together concretely all the way from the idea to the application, and that's why I kind of suffered, I think, in the end of my PhD. So—but it was valuable to teach me to think about that, right, to sort of try and think through the end game application. And so I did think about that a lot, and that in fact was—it was transformative because I—two things happened towards the end of my PhD. One is that I met Eric Betzig, and we'll talk about that in a second. But the other is I went to Woods Hole, to this physiology course, and I went there because I had heard amazing things about it. But I also was interested in cell biology, so this was driven out of my desire to understand something about cells. And that was kind of transformative because it was obvious to me the impact that optical microscopy had on this community of cell biologists. And so I started to think this is where I want to be next. I want to build instruments that are useful in cell biology because these guys need it. There is this mismatch between what they can see and what they really want to see, and that was evident to me even before I met Betzig. It was the diffraction limit and the fact that there's this frustrating mismatch between the molecular scale and the cellular scale that was so clear from classes and from my own experience, right? Molecules look like blobs of fuzzy—fuzz on the camera, but I just didn't know what to do about it. I—the problem was clear.

ZIERLER: How did you know that it was wrong? How did you know that they shouldn't be fuzzy?

SHROFF: Well—

ZIERLER: How did you know that that's not just what they looked like?

SHROFF: So I—it's funny you say that. As a—as an instrumentation person building the instrument that you can actually look at these fuzzy blobs, it becomes clear this is what they actually should look like in the instrument. But then even before that in classes, you'd get [??] on the way if you take basic physics about diffraction and light. You're taught this at sort of an undergraduate level, but it doesn't become concrete until—at least for me until I was actually in the lab. And I was surrounded by protein—by people in biophysics that were more on the biology end, and these guys had built all these sophisticated instruments to make macro level hypotheses about micro level phenomena, right? The—when you think about something like the structure of DNA, right, that's something that you interpret and interpret and interpret, and then you make a cartoon of what you think is actually there at the molecular scale. And that gulf between the observable and the observed, that was evident to me even as graduate student. And so when I went to Woods Hole, it was kind of reinforced, right, that these guys were struggling to see diffraction-limited images of cell division. Everything they did was contingent on seeing things on a microscope with their eyes or on a camera watching these intricate processes inside a live cell. It was clear that if you could somehow impact what they could see, you would have tremendous impact, right, in this field. And so that sort of reinforced this idea that if you're building tools, you should go after a target-rich environment of people that can use your tools. And this coincided happily with meeting Betzig who rolled through Berkeley at the time. I was also kind of a little bit—

ZIERLER: Where was he before Berkeley?

SHROFF: Unemployed. So he was—

ZIERLER: Really?

SHROFF: Yeah, so he was at Bell Labs, became disillusioned with science, and was unemployed for a decade essentially dreaming up ideas, right, in Michigan before I met him. And then he had this idea which became his Nobel Prize-winning idea, which kind of set him back on this course. He got—

ZIERLER: And what was his background then? What did he start in in graduate school?

SHROFF: Applied physics—

ZIERLER: OK.

SHROFF: —at Cornell. Yeah, and then Bell Labs, and then disillusionment and sort of becoming an iconoclast [laugh] and then getting back into it. So there was some of that—I didn't really—if you Googled Betzig, there was no information even at the time, so this was kind of risky to me. But the other thing that happened is I didn't want to do a post-doc in the traditional lab again. There was this movement to get these Science and Nature papers by studying your molecular motor. A bunch of my friends were getting post-docs in high profile labs, and I didn't want to be like one in a crowd doing that, so I was wondering what to do for my post-doc.

ZIERLER: So Woods Hole was before or after you defended?

SHROFF: It was—so actually, at Berkeley there's no thesis defense. You just write a thesis, and then that's it. You get it approved, but it was before that. So I was—yeah.

ZIERLER: Really, there's no public—

SHROFF: There's no public thing. So we had a thing just to our friends that our program did, biophysics did, but there was no public defense, which is weird. It's just at Berkeley—

ZIERLER: Is there a proper dissertation committee?

SHROFF: There is. It—

ZIERLER: Who was on yours?

SHROFF: So my advisor and then this guy Bustamante and then two other big shots I think in chemistry and bioengineering, and those guys—

ZIERLER: OK. No outside reader? All Berkeley?

SHROFF: All Berkeley. Yeah, but in different departments. So this decision to go to Woods Hole was motivated by this kind of desire to learn something more applied. And then I met Betzig about a year before finishing, and I was kinda wondering what the hell to do with myself at that point. I—my PhD, I published some papers. It was kind of a failure, and then I didn't do what I wanted to do. I did want to do a post-doc like everybody else did, and then luckily, I went to the seminar where—I remember reading the abstract of the seminar, and I was like, "Is this guy for real? He's talking about beating the diffraction limit. This is crazy." So I went to it, and I'm glad that I did because I went to him—

ZIERLER: The seminar was at Berkeley?

SHROFF: It was at Berkeley in some—maybe bioengineering or something or maybe at—to LBNL, Lawrence Berkeley National Lab. It was not super widely attended because people didn't really remember who he was. There were—Steven Chu might have been in the audience. He won a Nobel Prize. Bustamante went. So people that knew Betzig from back in the day went but biologists didn't go. And so he ended up talking about something called the lattice light—lattice—he had this idea for building a high speed light microscope. He didn't talk about the PALM scope that won him the Nobel Prize because that was top secret at the time. The paper was still under review at Science, but the other talk that he gave was suitably amazing that I was like, "This is what I want to work on." He—this was a guy who was clear in his talk was thinking about biologists, right? He was a tool builder who was really obsessed with the idea of wide dissemination of his tool. So I thought, "This is a guy with vision. He obviously knows the technical details. I could really learn something from this guy." So I went up to him after his talk, and he said that he had this position in Janelia Farm. He was looking for people who—he said he was—there was some phrase that he used like, "People will be given every opportunity to fail." [laugh] And I was like, "All right, well, that's me. I will go after that." And so I went up to him after his talk and said, "I would love to do a post-doc with you," and that sort of launched the post-doc—

ZIERLER: Did you feel like you were maybe about to drink the Kool-Aid? You were OK with that?

SHROFF: Yeah, a little bit. I was worldly-wise enough to know that. I—half of me was thinking, “What the hell am I doing. [laugh] This guy’s an unknown. This Janelia Farm place is an unknown, but—"

ZIERLER: Yeah, what is this Janelia Farm?

SHROFF: So all he said about it was that it was HHMI’s biological Bell Labs. It had just started to—there were less than 50 employees at the time. It was not widely known. There was a website that they had put up about it, but it was in some backwater place in Virginia. So it was kind of a risk, but it sort of appealed to me also.

ZIERLER: Where’s the funding coming from for this?

SHROFF: HHMI. So they did not have enough ways to spend their money to maintain their nonprofit status, so they spent it on this Janelia Farm. So it was a bit of a long shot. People looked at me like I was crazy, right? But I—like, “Why are you going to Virginia near Dulles Airport to do a post-doc with this guy? No—he hasn’t published a paper in ten years.” But all of that kind of appealed to me. [laugh]

ZIERLER: And were you the post-doc there? Was that the idea?

SHROFF: One other post-doc from—that he had hired from Berkeley from a neighboring lab who I ended up talking to after I learned this before I went to work with him. So she and I were the two post-docs there.

ZIERLER: OK, and so what were you doing there?

SHROFF: So when I went to Janelia, I worked on PALM, his technique—so he had published this seminal Science paper in 2006, the year that I graduated Berkeley, along with two other groups. And so I went to work for him to work on what he talked about, which was not this area. But when this paper came out, it was so abundantly clear there had to be follow-up work on this technique that I was kind of that guy in his lab. And that turned out to be—again, I couldn't have foreseen this at the time, but it turned out to be a hugely strategic win for me because the work that I did was kinda foundational in applying this technique. And when I finished that work, I had no problem getting interviews for faculty positions. So I just—I totally got lucky. It was wasn’t—I did good work in his lab, but it was totally luck in some ways that I ended up with him on this project.

ZIERLER: When you were interviewing, did people know about this place, or were they just convinced of the work that you’re doing?

SHROFF: Well—oh, you mean—

ZIERLER: In terms of—when you said you were post-doc at Janelia Farm and you were interviewing afterwards—

SHROFF: Oh, yeah, yeah, yeah. So—

ZIERLER: —would people in the field know of this place or not?

SHROFF: They did. They did. At that point, there was enough good stuff coming out of there that people knew, and now I think it’s recognized to be a good place. But at that point, people started to know because of the quality of the work we and others were doing. So it definitely was on people’s minds. The technique was even more on people’s minds, right, this PALM thing that Betzig invented along with Harald Hess who was also at Janelia Farm. That was the thing everybody wanted in their own university and so on.

ZIERLER: Now, in terms of—are you thinking more about the practical application of this—

SHROFF: Yes.

ZIERLER: —beyond the lab? Are you sort of more focused in your thinking at this point?

SHROFF: Well, certainly, I—[laugh] well, actually, at that time, I had done so much of practical stuff. By practical, by the way, I just mean useful for cell biology. So the original Betzig Science paper was great proof of concept. There was some cell biology stuff in there, but there was a long way to go between making that something that you could just build in your lab. I was the person that kinda bridged that gap in his lab. I did a lot of the foundational study that made that bridging possible, but I was so sick of that technique by that point that I didn’t want to do that at NIH. I loved instrumentation. My experience at Woods Hole with Betzig showed me what an impact could be had in cell biology if you made advances in this area, but I didn’t want to keep working on that because I could sorta see the writing on the wall, that people were jumping into that field. And I didn’t want to be part of a bandwagon of that after my post-doc.

ZIERLER: And so your post-doc ends what year?

SHROFF: So I got there in December of ’06. I left in June of ’09.

ZIERLER: And this is a direct transition to NIH?

SHROFF: Yeah, yeah.

ZIERLER: OK. So one of the things I’m really interested in—what are you thinking in terms of—NIH is a very unique option, right, in terms of all the places that you could be.

SHROFF: Yeah, yeah.

ZIERLER: So what’s the big draw for NIH for you?

SHROFF: The biggest draw is the fact that you don’t have to write grants, and I was spoiled also at Janelia because you also don’t have to write grants as a PI. So I saw, working with Betzig, another model, right? Rather than having a gigantic lab and writing I don’t know how many R01 grantsto do biological research, instead having a smaller more focused group of people and working hand in hand with a post-doc, being directly related into the research. And by the time I had finished my post-doc, many of my peers had written these kind of transitional grants. I was aware that in a big research university, the PI spends a large fraction of their time writing grants, and I did not want to do that at all. And so the—that was—

ZIERLER: That's a waste of your interest and talents, you—as you said.

SHROFF: Exactly. Yeah, I was sort of confident that I could do it because many of my friends were doing it, but I just didn't want to spend that much of my time doing it. I would rather spend the time thinking about the science, working on the science directly than writing these grants.

ZIERLER: And is that truly unique to NIH in terms of how you think about this? Is this really the only place where you can sidestep—

SHROFF: There are a handful of other places, not many in the US. There are more models like this in Europe. So classic ones that come to mind would be the Max Planck discipline institutes, right, in Germany or EMBL is—or the MRC in UK, right? So they exist, but I wouldn't say that funding model is widely adopted in the US. There are a few places but not many.

ZIERLER: OK. All right, so you get here in 2009, and what's your initial position here? What are you doing?

SHROFF: Tenure track investigator. And in fact, I had talked to a lot of people before deciding to go the academic route, and one piece of advice that I got was not to spread myself too thin in the beginning. So I thought really hard about just a few things that I wanted to do. So I guess I wasn't completely telling the truth when I said I had completely abandoned this PALM thing. There was one thing I still wanted to do in PALM, which was to extend this to three dimensions. And so I did that as my—one of the first projects at NIH. I wanted to take what I had done in Janelia and apply this in whole cells as opposed to just one plane of a cell near the base of a cell. All of my work with Betzig was basically just doing one two-dimensional plane in very high resolution. I wanted to take recordings of entire cells at very high resolution. So I did that at NIH. That was one of the two projects that I started with. The other project was totally not related to what I did with Betzig. So when I was on the job market after my post-doc, I met a very talented neuroscientist at Yale, Daniel Colón-Ramos. Yale was the other serious contender, and part of it was because I met this guy who said, "You're building great microscopes. I have this great problem for you, which is I want to understand how the brain of this very simple organism, this worm C. elegans forms. I need a light sheet microscope to do it." And I proposed to build this kind of light sheet microscope. And so I wanted to work on a microscope that could image the development of every neuron, every brain cell in this developing organism, and so I started to work on that as sorta the second project when I came to NIH. And all of my work initially was just on these two areas.

ZIERLER: So it was only Yale? You really didn't seriously pursue other faculty positions?

SHROFF: Yeah, yeah.

ZIERLER: And what would your position at Yale have been?

SHROFF: I would have been a tenure track investigator in a cell biology department.

ZIERLER: OK.

SHROFF: And what attracted me—

ZIERLER: With the teaching requirements also?

SHROFF: Within a medical school. So relatively little teaching, but I would have had to have written grants. What attracted me about the Yale department is that the quality of the cell biology was superb. They had just gotten a new head of the department who would a year later win a Nobel Prize in cell biology, and this guy who was trying to recruit me was very serious about recruiting microscopists for this position. The one thing that scared me off Yale besides the grant writing aspect was that when I was recruited I got the feeling that I would be recruited to do PALM, what I did in Betzig's lab. Whereas the leadership here, they told me that when they hired me, they said that we don't want you to be doing the same instrumentation in five years, and that really attracted me because I was thinking along those lines anyway.

ZIERLER: What does that say about NIH culture, the fact that they gave you that message? What was your takeaway from that?

SHROFF: A great message. The danger of a place like NIH is ossification at the higher levels because once you get tenure, if there's no pressure to write grants, there's always a danger that you can just coast. Now, to some degree, that sort of deadwood is evident in any research university, but at NIH, I would think it might be worse than most because there's—you have these four-year review cycles, but they can't get rid of you, right, once you have tenure. And so I liked what was told to me, right, by the leadership at NIBIB. It seemed to me the right attitude that if you're going to give me a guaranteed paycheck or guaranteed resources, I better be trying to push the envelope. So it was the right message. Do something new, right, if you come here.

ZIERLER: Now, what did you see is the value of the 3D imaging? What was new about that? What was exciting to you about that?

SHROFF: Kind of at a trivial level, everything in biology is 3D, right? So we get away sometimes with abstracting to 2D planes, but there are very few biologists that would tell you if you couldn't get a 3D image without giving up anything else, they wouldn't want that, right? There's just much more information when you look at a cell, when you look at the things inside of a cell, if you can get that third dimension. Otherwise you're limited to inference, right, about how things might go. Now, if you're imaging membrane proteins like on the surface of a cell, 2D is fine, right? And there's a lot of great science that happens in 2D in that system, but if you're thinking about more macroscopic phenomena like how groups of cells interact with each other, this is fundamentally a 3D problem, right? Organisms are built cell by cell in 3D, right? I mean, tissues are built out of cells in 3D and so on. So it was exciting to me because—to answer your question, it was exciting to me because there were not very good ways of doing that at the time. The classic way was this confocal microscope, which were commercially available but not—you sacrifice—there're tradeoffs in using confocal microscopes like more illumination dose, slower speed, and that—these tradeoffs could be alleviated by these light sheet microscopes that I and others are working and were working at the time.

ZIERLER: In choosing NIH, did you get the sense—NIH is by definition if you're a patient here, there's something interesting going on. There's research value. Was that something attractive to you as well, that there were going to be novel challenges that you would be exposed to here that you wouldn't see elsewhere?

SHROFF: What—not so specifically what—but what attracted to me about—what attracted me about NIH after Janelia was that NIH is super broad. So you can go to a talk one day about MRI, go to a talk on another day about coronavirus or epidemics. Janelia Farm is extremely focused, and I kinda missed the more general, global perspective after being in a very cloistered environment like the HHMI Janelia. I did not want to be there for a super long time, right? It was just too narrowly focused. So I liked the idea that at NIH I could have coffee with somebody doing science on a totally different thing. The clinical aspect was sort of a plus but not something that, again, I really thought that I would work on. Now we happen to have some work with some clinical collaborators, but it wasn't really something that I planned. It wasn't a bonus at NIH.

ZIERLER: Right. So—

SHROFF: It was the breadth of NIH that was more—

ZIERLER: Yeah. So you're not necessarily here—you're not interacting with a doctor who's seeing a patient where this is like some new issue and there's some new way that they need to be able—

SHROFF: Now I am.

ZIERLER: —to deal with it?

SHROFF: Now I am.

ZIERLER: Now you are.

SHROFF: At the time I wasn't.

ZIERLER: OK—

SHROFF: And it wasn't even on—it wasn't really on my radar. I knew that I could, but all of the questions that I had at those—at that time and still today are more at the basic level. So your basic meaning cell biology or model organisms like the worm or the zebrafish. Now I do work—we do have a collaboration with an actual doctor, a medical doctor, a surgeon who treats cancer patients that many of them will die. And this doctor has figured out a way of keeping their organs alive long enough we can take a piece of it out and image it on my microscope and get a resolution that he would not be able to do otherwise. So that—this is a collaboration that is—could have direct implication for the clinic.

ZIERLER: Which doctor is that?

SHROFF: Jonathan—

ZIERLER: Hernandez?

SHROFF: Yes. You talked to him or—

ZIERLER: My wife had hemangioma surgery with Dr. Hernandez—

SHROFF: There you go. OK.

ZIERLER: —last year.

SHROFF: So he actually—

ZIERLER: That's an amazing connection.

SHROFF: He actually approached me.

ZIERLER: Really?

SHROFF: Yeah—or no, no, somebody else connected us, and then we sat down and talked. So yes, that's the guy, Hernandez—

ZIERLER: I remember just talking with him about that 'cause I got the sense right away—

SHROFF: Liver?

ZIERLER: Yeah, liver.

SHROFF: Yeah, liver, yeah.

ZIERLER: Yeah. That's amazing.

SHROFF: Yeah, yeah, so that is something that is—it could happen in a well-funded research university with a medical school, but it was very easy here. Yeah.

ZIERLER: Right. OK, so the tenure process here, did you understand this as like a basic academic tenure process or is there a unique tenure experience at NIH?

SHROFF: It's very similar in the sense that what's different is that here you—well, OK. There are similarities and differences, so like outside, there is an external bunch of people that write letters. They're—what's different is that they also take external people here and fly them in to review you, and that happens even after tenure, and it's a good thing, right, because it sort of guards against this kind of ossification that I mentioned, right. So that—I knew about that process, and that's good. People take that seriously. It's rigorous. Then if all of that goes well, then there's an internal vote by PIs at NIH across many different institutes that look at your case. So my boss is responsible for presenting the results of this external review to the intramural community, and they make a vote similar to what might happen at a university. So they're—it's kind of similar.

ZIERLER: Now, do you build the lab before or after you get tenure?

SHROFF: When you say build the lab—

ZIERLER: This lab here, the lab that you created essentially, which happens first?

SHROFF: Yeah, so I would say that it's extended. It has become extended after I got tenure, but much of it was around as I was getting tenure. So within the first nine months when I came here, we didn't have any lab because it was being built for me. So my first nine months were in a conference room upstairs actually, and surprising amount of science got done. But then I moved that stuff, the instruments down here, and then maybe halfway through my tenure clock, I was doing well. There was a midterm review, so they gave me more space. They extended the space more, and then that's grown again since tenure.

ZIERLER: And getting tenure practically, how has that affected, I don't know, your day-to-day, but maybe your broader outlook in terms of what you do here?

SHROFF: The one thing that I hope—well, I actually hope that it doesn't change what I do too much because I don't view it—

ZIERLER: It's an external stamp of approval.

SHROFF: It's an external stamp of approval that makes my family life now that I have a small child more secure knowing that I have—we have a guaranteed salary, right? That makes a difference, but this—the family thing is relatively recent for me and when I was getting it, obviously I was nervous a little bit about it, but it was an external thing, like you say. I wouldn't say that it's dramatically changed the way that I do science. If anything, it makes it easier to say no sometimes for administrative stuff, but it hasn't changed the kinds of problems that I look at.

ZIERLER: Can you talk a little bit about your style as a mentor with all of the post-docs here? And clearly, you were the beneficiary of a lot of great mentoring in your education.

SHROFF: Yeah, yeah.

ZIERLER: So I wonder if you could talk a little bit about your style and how you sort of want to pass on that tradition, the kinds of advice you give to your post-docs.

SHROFF: So I would say that to that point, I've experienced kind of two extremes of mentorship. At Berkeley, I had a mentor that was pretty hands-off, which had its benefits, but the downside is that I foundered for a while myself, and with Betzig, it was too much the other way. It was extremely hands-on. There was just two of us in the lab while I was there, and this—he was in my face all the time, and it was too much. There was no—

ZIERLER: So there's a balance for you.

SHROFF: There's a balance for me. There was no capacity in his lab for developing my own ideas. Although I was happy to work on his ideas because they were so good, and it paid off for me clearly. There's a balance here, right, that I try and invoke. I don't want to say that it keeps me up at night, but sometimes it does keep me up at night worrying about my post-docs futures because there's no guarantee that they can get an academic job. It' s difficult out there, right? Raising money is hard. And so it worries me a lot when things aren't working, and I want to know about the failure so I can help them with things as they don't work as inevitably there'll be problems. So I'm fairly hands-on in that approach. I want to know what's happening to their projects, but I won't get in there and build instrumentation with them unless they ask me to, and most of them don't want me to at this stage. I would say that I've been here now for a decade. My approach has been getting steadily more hands-off, but I still think I'm more hands-on than many people that I know, my peers in the university system that have to spend time writing grants. What has changed for me is that now I have more people than I had in the beginning. So in the beginning, there were just three of us, me and two staff scientists, then were more. So in the beginning, I would work fairly closely. I would prepare samples myself. I would image things myself and analyze data to the level of writing pieces of code measuring things, right, and that part of it has tapered off. But I'm still highly involved in the project planning, and I want to know if there are problems when I—so I usually tell people when they interview, I'm not an asshole, but I do tend to be megalomaniacal about my approach to research because this is your time, this is your future, and you're choosing to spend time with me, right, so we want to make sure that it's spent well. I try and look for failure points and stress points. I want to know if something isn't going to work, why, and is there something that can be done about it, and if not, maybe we should find something else for you to work on. So that's the level at which I would say that I'm fairly involved.

ZIERLER: So when you see a post-doc spinning his or her wheels, what's your game plan when you go in and you see that? First of all, how do you know they're spinning their wheels first?

SHROFF: So yeah, without naming any names, in one case recently, somebody became so progressively more upset, it was—I—which is bad, but it was reassuring to me that this person is emotionally invested. But I think they took it one step too far. So I sat down with him, right? And I said, "Projects fail, but I think this is—I think you are a good scientist, and we will make something work." And so in this case, his project will work, but it was a question of finding the dead end. There are multiple ways of tackling a problem. Not all of them will work, and we're doing research, right, so we don't always know if every step—we might be able to sorta say from step A to D that this is a good goal, this is a good project, if you work on this there will be impact. But individual parts might fail, and so then there are backup parts. So we like to—at least I like to think of having backup plans if things don't work. In this particular case, some piece of implementation didn't work properly, and there was some good reason for that. There was some drift elsewhere in the optical system. So we—together we found a way around this. Almost all of the time that's the way it goes. There is some solution, but there have also been cases where there is no solution or none that we could pick up on. And so I like to have a few ideas—

ZIERLER: But there's value in that also—

SHROFF: There is. There's—

ZIERLER: —knowing when you hit the dead-end, right?

SHROFF: Absolutely. In fact, almost every successful—really successful thing we've done has come out of frustration at failure, right? So having some failure and thinking why is this microscope not right for this sample or why is this technique failing for this reason—that's usually where you have impact, right, in the long term. I gave a talk a few years ago where I was asked to talk to a lot of PhD students in bioengineering, and they asked me to include some of this perspective. So I had a few slides on my failures, which I was happy to list for them, and it was hopefully enabling for them to see that, right, because you don't see that a lot of times, right? And a lot of times our frustration or failure in one mode of microscopy has forced us to innovate, to make something better. Now, it's hard for post-docs to see that because they're on a shorter time scale, and the other thing that I try and remember always is that my perspective with every year gets broader, right? For me to have a project fail, it's no great shakes, right, because I have a portfolio of projects. But for a student or a post-doc, this is what they're doing, and so I—that's what keeps me up when I think about it. So I'm also kind of emotionally invested in their project, and I don't—even though I realize that failure is important, I don't like it. It's uncomfortable for me as well. And so I feel for them. I—yeah, this is their career, right?

ZIERLER: Right. So I want to return to this concept of there's greater interaction between you and medical practitioners now. Generally, are they coming to find you, or are you going to talk to them because one of the things that must be motivating you right now is with these instruments, you want them to be used, right?

SHROFF: Absolutely, yeah.

ZIERLER: They don't just exist as museum pieces. So what are you doing to ensure that they're being used and that they're getting feedback, this is what's useful? How does that process work?

SHROFF: I'm so glad that you mentioned that. So—because it is something that I take very seriously. One thing that I've done because of my experience with—at Woods Hole is that I actually take my instruments there. So I have this history of doing that every summer of taking an instrument in a U-Haul from here up to Cape Cod, and so that's a way of interfacing with the external community.

ZIERLER: You got to film it. That sounds like a documentary right there. [laugh]

SHROFF: Yeah, yeah, yeah. In fact, in India, there—

ZIERLER: Hari and his microscopes. [laugh]

SHROFF: There was a bit of a documentary that I should share with you at some point where we filmed this over a few days—

ZIERLER: Oh, really?

SHROFF: —of students in a course in India putting together an instrument that we have in my lab that was enormously entertaining and fun for everybody. I'll—maybe I'll send you that video at some point, but we do that at Woods Hole, and one of my former post-docs now is there. He's an instrument builder too. So I feel pretty good about that sort of way of disseminating stuff that is homebuilt here, and people come from all over the world there, right, to use those instruments. Now, at NIH specifically, this is valuable and not just for the external community, but also selfishly, it's good for me because I learn from the things that don't work. So I want to have this interaction in biology. So one thing that I did is that I petitioned the scientific directors at NIH a couple of years ago for some funds to build this advanced imaging and microscopy resource where I donate microscopes from my lab to this other space, and we have staff that are basically actively all the time collaborating with external folks at NIH. So this is one mechanism that goes outside my lab where the instruments are just there and can be used for biological collaborations, and people are well aware of that now certainly within the NIH and even some with outside the NIH. So that's one way that I kind of disseminate these instruments so that they're used. And then people do email me about them, so that—over the years, as the reputation has increased, that's one way that people have—but I don't—well, I do email people for collaborations, but mostly in the context of stress testing some new piece of technology that I made. So if we come up with something new, we want to throw the kitchen sink at it for ourselves and to show the community that it's useful as part of the scientific publication process. And then I do reach out to people, to my neighbors at NIH that are biologists and even people outside the NIH. So in the case of this worm collaboration, we have strong collaborators at Yale and at Sloan Kettering that we—they send us samples, and we image on some of these new scopes. And those—they in fact have cloned microscopes from my lab over there. So dissemination of what I do is a big part of it. That ranges from filing intellectual property at NIH—several of these systems have been commercialized, but that takes a while, right? There's always some lag, and some instruments are sufficiently complicated or the market is too small. They will never be commercialized. Thus the trips to Woods Hole or putting them in this facility next door to my lab. So we sort of take a multitiered approach to this. It's not just bringing people into my lab. That's sort of not enough, right, because then if all we do is just have people come to my lab, there's only so much you can do, right? You get a few nice papers, but like you say, we want them to be broadly disseminated, so we try all of these different approaches.

ZIERLER: And then to get that feedback for what works and what doesn't work.

SHROFF: Absolutely. Yeah, so there was one excruciating summer at Woods Hole where everything on—we had built this light sheet microscope and published a nice paper in Nature Biotechnology, but we wanted it to be used. So there was this poor post-doc who now got a faculty position at Woods Hole whose job it is—was to try and make the next generation system. So we put that in a U-Haul and took it to Woods Hole and nothing worked. Everything failed from this transitional instrument to just people putting samples on the instrument. They—there was a much greater variety of samples people put on the scope, and that was very educational but difficult at the time. So I take that very seriously, this idea of finding samples that break the scope.

ZIERLER: Right. Are there things that you want to accomplish with your instruments but the technology or the engineering isn't there yet?

SHROFF: Yes. Yeah, so particularly in this worm embryo, we've made, I would say, impacts in what you can see inside the worm. So it used to be you couldn't image these embryos without killing them, and our instruments have now made it that you can. You can image the whole development from when the thing is like a two-cell embryo to when it's a little worm and then hatches. But you show that to a biologist, and they're kind of amazed, and then they want more. They want more resolution. And so there's this constant fight between hitting physical limits and then getting the biologist the resolution, in this case, they need. And I keep thinking we've hit the end of the road. There will be no more, and then there's something new that comes up that sort of changes the game. So most recently it's these neural networks, right, that you must have heard about, these artificial neural networks that are finding impact certainly in computer vision but also in microscopy. So in microscopy, if you have some imaging sample and some constraints, you can only put so much light on a sample before it dies, and that means you can only get relatively coarse resolution. But if you can build a neural network that can infer the high resolution from a low resolution and a high resolution dead sample, you can apply that neural network to living samples. So there are these new computational tools that are very powerful that I think may yet again allow us to push further into these technical goals that are sorta physically constrained. Does that—

ZIERLER: Yeah. So those are computational limitations that you're excited about? They're not necessarily engineering limitations?

SHROFF: So exactly. So I would say that we're constrained in what I do by the fluorescent dye. Ultimately the fluorescent dye will only give off so many photons before it is bleached and destroyed by the incoming light, the radiation we put on it. When that happens, the experiment is over, and so a lot of the art in microscopy right now is partitioning the existing fluorescence photon budget. The sample gives off only so much fluorescence, and you can partition that in space or time or in dose, in imaging duration, and—but then you're—that's kinda fixed, right? And you can build clever microscopes that make better tradeoffs, but ultimately, you're constrained by physics. These artificial neural networks let you sorta bend these boundaries a little bit because you're using priors, you're using data, statistical priors to infer information about a sample based on what you sort of know that it looks like from imaging other specimens. So that lets you go further in microscopy as well. So I'm excited about that.

ZIERLER: OK. All right, I think we're gonna transition to the big questions portion of the interview. So first, are there fundamental principles in science that are just sorta like you just keep returning to day in and day out, things that—from physics, from chemistry, from biology? What are the big fundamental principles in science that are just like bedrock for you for doing what you do?

SHROFF: For doing what I do specifically, I—wave optics, physical optics, which is basically an outgrowth of Maxwell's equations in physics. These are bedrock upon which my field is built. They tell you sort of from day to day what's possible, what isn't. So this would be an area of physics optics that we use every day. That's kinda bedrock for me.

ZIERLER: So give an example of what you learned in a textbook 20 years ago and how you're just relying on that knowledge in the lab working on your instruments.

SHROFF: Day-to-day, ray optics—that's gets you surprisingly far. So in a textbook, in physics, the third physics class that I took in college, in an optics lab, those fundamental principles are still what I use from day to day. So if we want to build a new microscope, the nuts and bolts of that would be putting lenses and mirrors and lasers together in an optical configuration. We rely on decades of optical physics and optical engineering for that piece of what we do. So there's very little creativity in that part. Most of the creativity comes in in sort of seeing how much of the physical optical theory that we learn in textbooks can be bent by using fluorescent dye molecules. So the Nobel Prize in super-resolution microscopy that Betzig and Hell and Moerner won was given for not circumventing the diffraction limit, which is a textbook example of what we all use and think about every day, but using things that people back in the day couldn't possibly have known, in this case, the properties of fluorescent molecules, the fact that they can be cycled between a dark state and a bright state. Even that is sort of like a chemistry textbook principle, right? You learn about these different states of molecules in quantum mechanics or in physical chemistry or in organic chemistry, but the creativity was putting this together with kind of a different area of physics and realizing what could be done. So for me, I would say that I rely on undergraduate level physics and optics sort of every day, and a lot of the creativity comes in blending these things in ways that people have not thought about in synthesizing sort of the chemistry and the physics. Does that sort of answer your—

ZIERLER: Absolutely.

SHROFF: —question? It's very rare that we or even, I would—I dare say, other people come up with an idea that is totally novel. [laugh] You'd find derivatives of these ideas and the optics literature going back decades.

ZIERLER: Is there anything that you have found in your lab work that makes you question any bedrock principles of physics? When theories are—I don't know—disproved is maybe too dramatic, but where bedrock theories can be improved upon because you're doing things that nobody else is doing, right? In other words, it's a two-way street in how physics worked, right? You're bringing the theories and the concepts to a practical applied level.

SHROFF: Yes, yes, yes, absolutely.

ZIERLER: But in the course of doing that, my question is, are you contributing back to those theories and improving them in and of themselves?

SHROFF: Those theories, relatively little. There has been some stuff specifically in the microscopy area which we have done that changes the way people think about confocal microscopy. So there is a textbook version of the confocal microscope that—parts of that—we're not getting too technical. That description is kind of dated. So we and other labs have contributed to updating our notion of what it means to build an efficient microscope where you extract everything you can from the image. I would say that those ideas, which have been around for decades, are a little bit old, and those textbooks have to be rewritten or revamped, let's call it. but as far as the bedrock upon which that's sitting, that's pretty rock solid, and we have not fundamentally changed that sort of level of strata. The area in which we—which I think there's real opportunity for us is in using these new tools to fundamentally discover new things about living systems. And there's a physics of living systems as well, right, that is kind of nascent, right, about sort of self-organization and how these things connect and come together to form highly complex behavioral machines, right, these things that defy entropy to kinda carry out tasks while the organism is alive. We have—what excites me is the opportunity to use light microscopy to study these in a level of detail that would have been impossible 5 or 10 years ago. So that's not contributing to kind of textbook level optical theory but is contributing to new knowledge that could change our way about how we think about living systems. That's really exciting in sort of a big way. So it's very applied, I guess, right? It's not unseating fundamental optical theory.

ZIERLER: On the question of coming up against new knowledge, what is your basic philosophical stance to the idea that the more you know, the more you know you don't know?

SHROFF: I mean—

ZIERLER: Is there an infinite—is there just an infinite amount to understand about the physical world, and you just have a special privilege of being able to peer at a deeper level than most people?

SHROFF: The short answer is I don't know the answer to that question. It could be like the layers of an onion. You just keep peeling away, and there's more and more. Or it could be that we get a—we—especially biologists get to the point where they're sorta satisfied they have some mechanistic understanding of the molecules involved and how those molecules interact with one another. As far as that really big picture idea, I really don't know. I do think, though, that we're in this era of big data, and the thing I worry about is information overload. It's very easy, especially in my field, to push a button and accumulate terabytes and terabytes of data without getting any more real insight into the underlying biology even, right, forgetting about physics, the underlying biological mechanism as to why this is—how this is happening the way it is. So that's a real problem in my field specifically, and I do worry about that.

ZIERLER: Now, I know you have an interest in deep learning.

SHROFF: Yes.

ZIERLER: Now, is deep learning the antidote to this issue that you're concerned about?

SHROFF: Well, not necessarily because you can apply this black box without really understanding how the deep learning engine is working, right? You could not understand in a deep level what these software program's doing. I mean, at sort of an extremely general level, I could describe to you the math in a neural network, but as far as what that neural network is doing in every layer, it could be some highly abstract thing that it's doing to learn a pattern in the data that may be useful to me without revealing any understanding of what's going on. So I don't think that's necessarily an answer. I view deep learning as sort of a convenience, right, of a way of sifting through mountains of data to find patterns that might be inconvenient to do any other way. But I don't know that it's necessarily an answer to this problem of massive amounts of data distilled into meaning. It's a way of—to take a very concrete example, in an image—if I take an image in one of my microscopes, there may be certain things about that image that I want like the outline of a cell or where the nucleus is or where some organelle is or where the head of a worm is. And I think there's tremendous potential for deep learning to give that to me quickly in a way that I don't fully understand, though. I don't know exactly what it's doing to say this is a cell membrane, right? I—that's not really what I'm interested in, though, right? What I'm interested in is a much more difficult question of if I have everything that I could get out of my image, how does that influence some biological theory of how the organism is making itself. That's the level of understanding that I'm interested in and that I think just having lots of data doesn't necessarily get it to you, right? That's the thing that I worry about, I guess. I worry about having reams and reams of data, extracting some features from the data via deep learning but then not necessarily knowing what to do with that. That—to me, I have a hard time seeing how deep learning could help us with that meta level of understanding, but that's what we want.

ZIERLER: Right. Is data helpful or harmful to getting us closer to what we talk about a unified theory in physics?

SHROFF: I think—I don't know about—enough about unified theories. I think if you talk to a particle physicist, you get a very specific sense as to what they mean when they talk about unified theory. So I don't—maybe I won't comment on that because I don't know that much about it, but as far as a unified theory of biology, there's a long way to go. And getting better tools and more data could be very helpful. The challenge is going to be parsing that data.

ZIERLER: Do you see such a thing as a unified theory in chemistry and in biology? Or are those subsets of the unified theory of physics?

SHROFF: If you talk to some physicists, they'll say that with Schrödinger's equation, it's basically all details all the way down, which may be true. You have this equation that describes matter, but I think a biologist would want to know fundamental questions to me, it seems like, that I don't see us getting from the Maxwell's equations or the fundamental model or something of—in particle physics. For example, if you want to know the basic rules that instruct a brain to wire itself from its component parts, we don't have that. That's a question you can ask, right, and you could reasonably expect to find an answer, but we don't have it. And so how do we get that answer? I'm not seeing it from the super basic sorta physical equations, right, that describe matter even though they must describe this kind of higher level phenomena. I see a huge gap there, which is very exciting, and I don't think we're gonna run out of problems like that anytime soon. Yeah, and I don't view that as necessarily a problem of—philosophical problem. I think this is a good thing. There's no shortage of problems like that. How does a neural network go from a bunch of independently firing cells to something with cohesion, right, something where cells fire together? Nobody knows, right?

ZIERLER: Yeah, yeah, but—

SHROFF: Even for a worm.

ZIERLER: But it's knowable? You think it's knowable?

SHROFF: I feel like that's knowable.

ZIERLER: And the—what gets us from here to there is what? Is it imagination? Is it technology? What are the big things, the big hurdles?

SHROFF: I think it's both, but I think—to get back to data, I think it's partially data. I think we don't have—

ZIERLER: Put out too much data. [laugh]

SHROFF: Yeah, exactly, but not—but—well, the right data.

ZIERLER: Right—the right data.

SHROFF: The right data. The right data. So the trouble with biology is you can cast around a lot and get the wrong kind of data. To give an example from the '50s, right, the 1950s, the central dogma of biology, people were able to uncover the amino acid code not by studying some complicated biological phenomena. They studied bacteria. They studied a model organism which gave them the right kind of information, right, to attack these fundamental problems of molecular biology, how is material transduced from DNA to RNA to proteins. This is a basic biological theory that underlies a lot of other stuff that you wouldn't get if you had the wrong kind of data, and I think it was Crick or Sydney Brenner or something that said that they were studying these very basic systems, and they thought most everybody else was doing it wrong. I guess that's what I worry about a little bit in biology, right? Probably most people are just doing it wrong.

ZIERLER: Yeah. [laugh]

SHROFF: So—and that's because we don't know how to do it right.

ZIERLER: Yeah, so what's the feedback mechanism? How do you know when you're doing it wrong? How do you know when you're doing it right?

SHROFF: You try and look for unexplored areas of biology, murky areas that are underexplored, and you try and look for lots of—you try and encourage behavior where there are lots of mutations. That's what you try and do. And I don't know—that—part of this is a policy thing, right? How do you encourage that kind research of trying to get away from the grain, right? You—fields start to get boring for me when there are lots of people into it. You don't want to be in bandwagon type science, and if you look at many, many historic discoveries—I'll give you another one. CRISPR, right, is another discovery that is making waves. These guys didn't know they would hit up on that tool, but it's a hugely useful tool that people got by studying sort of esoteric stuff. So I guess what I would say is study esoteric stuff, study marine organisms or study worms or flies or things that are not sexy, right? There is this impulse to study in biology clinically relevant phenomena, which has its place, but I don't think we're gonna get the answer to the big questions by studying things that are sort of obvious from A to B. The human brain is kind of intractable right now with today's instruments for studying these basic questions.

ZIERLER: Yeah, OK. Some retrospectives on your career so far. Are there things that you wish you had an opportunity to return to and do better? Or do you kinda feel like teleologically, right, the mistakes, the shortcomings, the failures, the dead-ends all had productive value because they led you to where you are and what you're doing now?

SHROFF: They all had productive value. I think the essential thing is to make mistakes and thing about ‘em, think what—think about what can be learned. I couldn't—I just couldn't—

ZIERLER: So introspection is fundamental to good science?

SHROFF: I think introspection is constant in my mind. I am always thinking about things that don’t work or things that I would like to do and why I can’t do the things [laugh] that I want to do like in microscopy, why can’t I build this instrument. In some cases, physics intervenes, and there’s nothing you can do, but I keep them sort of in the back of my mind because maybe in five years, somebody else will come up with this tool that I can adapt for my purpose. That kinda thing I think is essential in science. And we’ve just seen that—I’m just a young buck. I’ve only been [laugh] doing this for like a decade, but there’s so many examples where I’ve seen that happen just in the last ten years. In fluorescence technology and fluorescence dye technology alone, right, somebody will make something, like a biochemist or a chemistry, that I could use to enable microscopy, right? So that sorta thing is introspective. No, I couldn't ten years ago have connected the dots. I have no idea how I ended up here. I could not have predicted this. So one thing that always amuses me is this notion of the five-year plan. When I interview for academic jobs, people ask me, “What is your five-year plan?” I had to be honest. I said that, “Look, I think on maybe the year or two-year timescale. I can’t think that far ahead.”

ZIERLER: Yeah, yeah. Now, that's the limitations question. The success question—and if you want to hide behind what others say about you and awards you’ve won in your tenure application and things like that, what do you see in your work that has really moved the needle, that really has pushed the ball forward in scientific understanding so far? What do you see in that, the headline bullet points?

SHROFF: So headline bullet points, again, better microscopy. So if you can give a biologist a tool that lets them see something they couldn't see before, fundamentally for me, that's it, right? If they have some process they’re studying but because of a lack of a tool, they can’t get at what this particular protein is doing inside a cell, if I can give them a tool lets ‘em do that, for me that's enough.

ZIERLER: So that means that you have moved the needle on diagnostics mostly?

SHROFF: On diagnostic but also mechanism. What is this thing doing inside a cell that results in some biological phenomena? So you can call that diagnostics if you like. I guess I think of diagnostics more in sort of a medical context, but yeah, I mean, giving a biologist a tool that lets them advance their study of some biological phenomena, that's the way in which, broadly speaking, my work—that's the best thing that I could do because I don’t think I’m going to be unseating some prevalent optical phenomena. That's sort of not really what we do so much. There have been instrumentation advances that are significant that we’ve done. We have improved the performance of a confocal microscope fundamentally, which is a workhorse in the field. So one of my former post-docs and I did this, and I think that's having a broad impact in the field of microscopy.

ZIERLER: And how are you hearing about that? How are you hearing about this positive impact? Who’s coming to you and with what news that makes you feel good about this accomplishment?

SHROFF: So there’s commercial impact. These technologies have been commercialized and some of our proudest moments come when people we’ve never heard of are publishing papers using our method or adopting our technique without any help from us. In some sense, then we’ve succeeded, right, because it’s having a life of its own.

ZIERLER: You’ve given them the blueprints.

SHROFF: We’ve given them the blueprints, and they’ve successfully replicated it without my name on their paper. That's great. So that’s a good sign. When I see some high profile biological study or something, right, using a tool that I made, that makes me feel good about what I’ve done.

ZIERLER: Now, it’s such a unique opportunity for you ‘cause you have hopefully decades of work ahead of you, right? [laugh]

SHROFF: Hopefully, hopefully. Yeah, yeah.

ZIERLER: So what are the big goals for you? What are the things that you’re excited about? What are the challenges where right now it seems insurmountable but at least you have the perspective and the imagination to say 10, 20, 30 years, I think we can conquer these things?

SHROFF: I think one thing that I’ve been thinking about again in the context of neural networks—so you’ve heard about these guy that can make a computer program beat the best human at chess, right, or at Go or something, right? So I—there are a lot of practical struggles that are holding biological research back having to do with the way that microscopes operate. Why can’t we make our microscope sort of treat the microscopy image process like a game that could be optimized by the microscope itself? I see tremendous future for smart microscopy. In other words, when I think about the amount of time we and others waste in optimizing the microscope for some particular sample, that seems to me to be something that could cry out for automation. There is a right way of performing an experiment when it comes down to the kind of tradeoffs or the performance metrics of the microscope. If you want to image a sample with this much signal-to-noise ratio or with this much resolution, given feedback from the sample as you’re imaging it, there’s no reason why that couldn't be more automated, and this could accelerate science. So this is sort of like an engineering viewpoint of something that I see that in 20 or 30 years if the right effort were put on this area, microscopy, generally speaking, could be improved.

ZIERLER: So better microscopy means better what beyond microscopy? Better health outcomes? Better—you tell me.

SHROFF: Beyond microscopy, better health outcomes, less wasted time imaging samples, and more information-rich microscopy datasets. So to give it a concrete example with health, people—we still rely on people looking at H&E stains to get information to inform some prognosis, right? That's a very clinical aspect, but you can imagine a similar thing when a biologist uses a microscope to look at their sample. They’re looking at some particular thing like a cell dividing, right, and they want to know from the image some feature of that cell as it divides. There’s no reason why we can’t just get that in a single shot. There’s no reason why the—maybe you could argue the biologist should always look at the image, but they’re look—they’re extracting some feature of the image, right, that could be learned by a neural network. So I think there’s tremendous opportunity to go end to end for having the biologist put the sample on the microscope, the microscope do its thing, and then they give the biologist the answer. So the biologist wants to know how many of x things are in their sample, how many tumor cells there are in a tumor, how many nuclei there are in their sample, how many cells there are, how many membranes, etcetera. We should be able to get that information for them without the biologist intervening at all.

ZIERLER: Are you involved in all the larger project and minimizing biopsies through better imaging?

SHROFF: Somebody has talked to me about that. I'm kind of less interested in that. That's very applied for me, but I've talked to people that are interested in that, and I see some of the fundamental problems there, the same as many of the biologists that want to know something about their image. There is this—we have been optimizing microscopes to get pretty images, to get images that are information-rich, but what does that actually mean for the end user, right? At the end of the day, they want something out of the image, and so I think if one could understand better what they want, there's no reason why we couldn't just give it to them after the image is acquired. So there is tremendous opportunity there in what I'd call end-to-end imaging where you circumvent the image analyst or the person that denoises the image or restores the image or—there's this thing called computational microscopy where you take a bunch of images that don't look like anything. They look like garbage, and then you apply a computational program to recover something that looks pleasing to the biologist, that looks like something you or I would interpret as an image. But why, fundamentally, do we need that intermediate step, right? At the end of the day, it's some human evaluating what the microscope is telling you, and I think that one could short circuit a lot of that once we decide what information is relevant at the end of the day. And this could have profound implications whether it's biopsies or something more like fundamental research. Does that sort of make sense?

ZIERLER: Yeah.

SHROFF: That's—I'm making an automation argument but in a very specific way because I think we can learn from what DeepMind is doing. These guys are playing games, but there could be tremendous opportunity for science for getting what the biologist wants by using these tools, right, that these guys are making for other applications.

ZIERLER: Are—but both scientists are probably not thinking about game theory, right?

SHROFF: They're not. They're not. They're not. So there's an opportunity for—sometimes breakthroughs happens in science when you get these groups of people talking to one another. And I think that's an area of opportunity because biologists are not thinking this way at all, and in fact, even when I talk to computer scientists, they're more interested in sort of algorithms, right, in making the best next neural network. But there is this intermediary space where I think there is tremendous opportunity. There's a gap. There's a gap. There's a technological gap there where people that could speak both languages have opportunities.

ZIERLER: Right. Right. OK, I think I'll ask the final question. Are there mysteries that seem as mysterious to you now as they were when you first started as a 14 or 15-year-old? And does that lead you to think that these are just mysteries that are beyond human capacity or even human machine capacity, that are just areas of things that are knowable but they cannot be known to us?

SHROFF: Yeah. The—yeah, so—

ZIERLER: Or is everything fundamentally knowable? It's just a matter of time to get there?

SHROFF: Ooh, I—yeah, I—the reason I'm struggling here is that I don't really have any good reasons for my intuition that I can readily give you. I sorta feel like there must be things that are knowable that for complexity reasons alone are just very difficult to get at, right, like predictive—

ZIERLER: I'm asking you specifically because your whole business, right, is peering into the known—into the unknown and finding out what's there and then knowing it.

SHROFF: Yes.

ZIERLER: So I guess my question is, how far forward can you stretch this process?

SHROFF: For things in my work specifically that require you to know where every single molecule is to understand that process, that's pretty hard. It's pretty hard to imagine a tool, an optics tool that will give you that level of precision inside even a single cell in a living organism. So that—I view that as a technological barrier that may or may not be surmounted in the future, but I have a hard time seeing it now despite the Nobel Prize that was given in super-resolution microscopy, right? So people got a Nobel Prize for saying this diffraction limit is not fundamental, but I think there are huge practical problems in knowing in vivo in a living cell much less a patient or an organism where everything is. That's a very basic thing, right? You might want to know where are all the molecules in some cells in a tumor in a human. That seems like a difficult thing to know. Fundamentally, it seems like it's hard to imagine a measurement device that could give you that. So I—

ZIERLER: And it's staring you right in the face.

SHROFF: And it's staring you right in the face. This is something—this is not something like in space or in the universe. This is very, in some sense, prosaic but hard to get a handle on. So there are problems like that I view as really, really hard, and my approach to that problem has been to study phenomena that are—that you have some line of attack. So I like to think about model organisms. I like to think, "What is the E.coli of the brain, right? What is the simplest organism that I can study?" So there are a lot of people that are interested in studying mouse brains or monkey brains. For me, that's way too hard for my lifetime, right? I can't think of understanding a mouse brain in my lifetime, but [laugh] maybe in my lifetime I could understand a worm brain, maybe.

ZIERLER: [laugh]

SHROFF: So I guess I would answer you in—by this way, that in biology, the parts number is still so fundamentally vast as it was when I was 14 years old, and there are molecular questions there that I think would be really hard to get a handle on.

ZIERLER: Right, and I think that's something, it sounds like, just from the energy and passion you bring—that's not a dispiriting realization. That's something that motivates you to keep acting.

SHROFF: It's an encouraging challenge to think about, yeah.

ZIERLER: Yeah, OK. Well, Hari, thank you so much.

SHROFF: Well, thank you. [laugh]

ZIERLER: This has been a delight.

SHROFF: OK, good.

ZIERLER: There are gonna be so many people who truly will get so much out of this oral history, and I really appreciate your time today. So—

SHROFF: Thank you very much. That was fun.

ZIERLER: —thank you.

[End]